REMARKS

Reconsideration and reexamination of the subject application are respectfully requested in light of the foregoing amendments and following remarks.

1. Status of the claims

Claims 1-27 are pending in the application. Claims 13-17 and 26-27 are canceled by entry of the present amendment for the sole purpose of expediting prosecution. The claims are canceled without disclaimer of any subject matter and without prejudice to Applicant's right to pursue the canceled subject matter in a later filed continuing application. Claims 1-12 and 18-25 are pending reconsideration and reexamination.

2. Support for the amendments

Support for a derivative of an agnoprotein, wherein the amino acid sequence of the derivative has at least about 83% sequence identity to SEQ ID NO: 1 and has cell growth inhibitory activity is provided at least at page 5, lines 15 and 20, of the specification. Further support is provided, for example, by the agnoprotein consensus sequence set forth in SEQ ID NO: 13, which has a sequence identity of 85% with SEQ ID NO: 1 (Exhibit 1), or by the agnoprotein sequence of SEQ ID NO: 22, which has a sequence identity of 90% with SEQ ID NO: 1 (Exhibit 2). "Sequence identity" is defined in the specification at page 8, line 17, *et seq.*

Support for the amendment of claim 12 to recite "glioblastoma" is found throughout the specification, including the claims as originally filed. It is well known that a glioblastoma is a form of cancer, particularly a cancer that has its origin in organs or tissues from the brain and spinal cord, as recited in original claim 15. The amendment is further supported *ipsis verbis* in the specification at page 18, line 26 ("glioblastoma").

3. Information Disclosure Statement

Applicant appreciates the consideration of the IDS filed January 31, 2005.

4. Objection to the specification

The specification is objected to for containing embedded hyperlinks. The amendment to the specification deletes the hyperlinks, mooting the objection. To expedite prosecution, the amendments further delete a hyperlink in the paragraph beginning at page 8, line 17.

5. Claim objections

Claims 7 and 21 are objected to for referring to sequences without an accompanying sequence identifier number (SEQ ID NO). The appropriate SEQ ID NO is added by amendment, and the objection may be withdrawn.

6. Rejection of the claims under 35 U.S.C. § 112, first paragraph (written description requirement)

Claims 1-5, 8, 12-19, 22, and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly inadequately described in the specification. Applicant traverses the rejection as it applies to pending claims 1-5, 8, 12-13, 16, 18-19, and 22, as amended.

The legal standard for written description

To satisfy the written description requirement, the applicant must convey to the skilled artisan that, as of the filing date sought, the applicant was in possession of the invention. *See Falkner v. Inglis*, 448 F.3d 1357, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991)). A description of the claimed DNA itself satisfies the written description requirement. *See Fiers v. Revel*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, 1605 (Fed. Cir. 1993). "To satisfy the written description requirement of 35 U.S.C. § 112 for inventions pertaining to DNA, a patent must provide 'sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' " *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 79 U.S.P.Q.2d 1813, 1818 (Fed. Cir. 2006) (quoting *Enzo Biochem Inc., v. Gen-Probe Inc.*, 323 F.3d 956, 964, 63 U.S.P.Q.2d 1609, 1618 (Fed. Cir. 2002)). Mention of a representative number of compounds falling

within a genus may provide an implicit description upon which to base generic claim language. *Regents Univ. Cal. v. Eli Lilly Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997). However, it is by now well settled that

> . . . it is the binding precedent of this Court that [*UC v.*] *Eli Lilly* does ***not*** set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art.

Falkner v. Inglis, 79 U.S.P.Q.2d 1001, 1008 (Fed. Cir. 2006) (emphasis in original). The Office's reviewing courts generally regard the adequacy of written description in the same manner for claims relating to proteins as for DNA.

The specification complies with the legal standard

In light of the applicable legal standard, the specification provides an adequate description of the genus of agnoproteins. The specification discloses that agnoproteins have been characterized in the art since the 1980's. Specification, page 2, lines 4-14. ***Over 100*** JCV agnoprotein sequences were known in the art at the time of the invention. Specification, page 13, line 7. The specification additionally provides six specific JCV agnoprotein sequences (SEQ ID NOs: 1 and 3-7) and four specific agnoprotein sequences from BK polyoma virus and SV40 polyoma virus (SEQ ID NOs: 14-17). Over 100 disclosed, representative examples of species within the genus of agnoproteins provides an implicit description upon which to base generic claim language. *See Regents Univ. Cal. v. Eli Lilly Co.*, 119 F.3d at 1569 (relying on *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) for the holding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process).

Applicant has disclosed throughout the specification that an inherent property of agnoproteins is the ability to inhibit cell growth. The specification further provides ***experimental evidence*** of specific regions of agnoprotein that are required for the recited biological activity. *See, e.g.*, Specification, Example 5. The specification thus provides

functional characteristics of agnoproteins falling with the claimed genus, coupled with a disclosed correlation between function and structure. *See Monsanto*, 79 U.S.P.Q.2d at 1818; *Enzo*, 323 F.3d at 964. The specification thus clearly provides an adequate written description of the genus of agnoproteins.

Further, the specification provides an adequate written description of agnoprotein derivatives having the recited biological activity and having at least about 83% sequence identity to SEQ ID NO: 1. The over 100 disclosed JCV agnoprotein sequences are sufficiently structurally similar to generate a ***consensus sequence***, disclosed in SEQ ID NO: 13. *See, e.g.*, Specification, page 13, line 5, *et seq.* The consensus sequence possesses at least 85% sequence identity to SEQ ID NO: 1, even where each alternative amino acid position is changed from the amino acid found in SEQ ID NO: 1. *See* Exhibit 1 (using BLAST to compare SEQ ID NO: 1 with SEQ ID NO: 13, where all possible alternative positions are different from the SEQ ID NO: 1 sequence, and using "sequence identity" as defined in the specification). The consensus sequence reveals amino acid residues that are conserved through evolution, which provides the skilled artisan with guidance as to which amino acids can be modified without the loss of biological activity. The other agnoprotein sequences disclosed in the specification have a similar degree of structural relatedness to SEQ ID NO: 1. *See, e.g.*, Exhibit 2 (aligning SEQ ID NO: 1 and SEQ ID NO: 22). Combined with the disclosure of the precise regions of an agnoprotein that are required for the recited activity (Specification, Example 5), the specification provides a more than adequate written description of the claimed genus of proteins. The rejection accordingly may be withdrawn.

7. Rejection of the claims under 35 U.S.C. § 112, first paragraph (enablement requirement)

All the claims are rejected under 35 U.S.C. § 112, first paragraph, as alleged requiring undue experimentation to make or use. Applicant traverses the rejection as it applies to the pending, amended claims.

The legal standard for enablement

There are many factors to be considered when determining whether the experimentation to practice the claimed invention is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

The specification complies with the legal standard

The presently claimed invention is directed *inter alia* to a method of inhibiting cell growth (claim 1) or treating a subject having glioblastoma (claim 12), comprising the use of:

(i) one or more agnoproteins,

(ii) one or more biologically active fragments of agnoprotein, wherein said one or more fragments comprise amino acid residues 1-36 of SEQ ID NO: 1, or

(iii) one or more derivatives of agnoprotein, wherein the amino acid sequence of said one or more derivatives have at least about 83% sequence identity to SEQ ID NO: 1, and wherein said one or more derivatives have cell growth inhibitory activity.

For the reasons set forth immediately above, the skilled artisan was aware of ***over 100*** agnoprotein sequences that are useful for practicing the presently claimed invention, evidencing that the state of the relevant art was highly advanced. Also as set forth above,

the specification provides experimental evidence of agnoprotein fragments that possess the relevant biological activity. As further set forth above, the specification, combined with the advanced state of the art, provides an agnoprotein consensus sequence. For the reason stated above, the consensus sequence allows the artisan to make and/or use predictably the claimed agnoprotein derivatives. Accordingly, the enabling teachings of the specification are commensurate with the scope of the presently claimed invention. *See In re Fisher*, 166 U.S.P.Q. 19, 24 (C.C.P.A. 1970).

With respect to the experimentation required to practice the invention, the specification further provides a number of routine cell culture assays useful to screen agnoproteins for biological activity. *See* Specification, page 30, line 1 *et seq.* (expression of agnoprotein in glial cells to assay an effect on cell cycle progression); page 32, line 7, *et seq.* (suppression of cell proliferation in NIH 3T3 cells); page 33, line 19, *et seq.* (using NIH 3T3 cells to determine the effect of agnoproteins on cyclins A and B, p27, p21, and p53, which modulate the cell cycle).

***In vitro* experimental results constitute a working example of the claimed invention**

Specifically with regard to a method of treating glioblastoma, the specification provides a working example of *in vitro* efficacy in the U87MG glioblastoma cell line. *See, e.g.*, Specification, Example 1. Efficacy in a cell model or animal model constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. *See* Manual of Patent Examining Procedure (MPEP), § 2164.02, "Working Example," 8th ed., revised Aug. 2006, under the subheading "Correlation: *In Vitro/In Vivo*." Whether a correlation between an *in vitro* model and a method of treating a disease exists must be determined ***from the perspective of one skilled in the art***—not from the perspective of the Office:

> If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)

> (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). MPEP § 2164.02.

In this regard, only a reasonable correlation is required—not a rigorous or an invariable exact correlation. MPEP § 2164.02 (citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)).

When viewed from the standpoint of the correct legal standard, the skilled artisan would have accepted successful tests for efficacy in the human U87MG glioblastoma cell line as correlating with a method of treating glioblastoma. Applicant submits herewith evidence from two research publications that chemotherapy drugs tested for efficacy *in vitro* using U87MG glioblastoma cells were considered candidates for further testing *iv vivo*. *See* Zhao *et al.*, *Int'l J. Oncol.* 21: 49-55 (2002) (attached hereto as Exhibit 3); Yoshida *et al.*, *Neurosurgery* 39: 360-66 (1996) (attached hereto as Exhibit 4). In each case, the skilled artisan used U87MG cells expressly because the efficacy of a compound in this cell line indicated the potential usefulness of the compound for *in vivo* treatment. *See, e.g.*, Ex. 3, p. 49 ("The present evidence that As_2O_3 at relatively low concentration effectively inhibited proliferation of U87MG and T98G cells *in vitro*, suggests that the drug may be considered for *in vivo* testing on animal models and possibly clinical trials on glioma patients."); Ex. 4, *2 ("This [*in vitro*] study was designed to determine whether the motility and invasiveness of glioblastoma cells could be influenced by treatment with [estramustine phosphate] and to correlate those findings with the ability of the agent to inhibit proliferation. Suppression of the infiltrative capacity of malignant glioma cells could be of significant value in the treatment of those lesions."). Nothing more can logically be required to find that the skilled artisan would find that the *in vitro* model "correlates" with an *in vivo* application.

The Office Action alleges throughout the rejection that successful clinical tests are required to comply with the enablement standard. *See* Office Action, pages 9-10. The Office has produced ***no authority*** that 35 U.S.C. § 112, first paragraph, sets forth a statutory requirement for applicants to provide successful results in a clinical trial for approval of a patent. To the contrary, it has been well established for over a decade that successful clinical trials are not a *sine quo non* for invention. *See In re Brana*, 51 F.3d

1560, 1568 (Fed. Cir. 1995) (reversing a rejection under 35 U.S.C. § 112, first paragraph, and holding that the demand for successful clinical trials is unduly burdensome and not required to prove even utility).

For all these reasons, the presently claimed invention comports with the legal requirements for an enabling disclosure under 35 U.S.C. § 112, first paragraph, and the rejection may be withdrawn.

8. Rejection of the claims under 35 U.S.C. § 112, second paragraph

(a) Claims 11 and 25 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Specifically, the Office alleges that it is unclear whether the recited derivative is SEQ ID NO: 22 or a derivatized form of SEQ ID NO: 22. Applicant respectfully traverses the rejection.

Although the Office must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach. *In re Morris*, 127 F.3d 1048, 1054, 44 U.S.P.Q.2d 1023, 1027 (Fed. Cir. 1997). The skilled artisan would understand the claims by their terms to indicate the former meaning. The antecedent basis for "the agnoprotein derivative" is found at "a derivative thereof" in claims 1 and 12, as amended. The antecedent basis for "derivatized form of SEQ ID NO: 22" by contrast would read "a derivatized form thereof." Further, the artisan would understand that SEQ ID NO: 22 is an agnoprotein derivative because it is at least about 83% identical to SEQ ID NO: 1. *See* Ex. 2. The rejection accordingly may be withdrawn.

(b) Claims 12 and 18 are rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. Specifically, the Office alleges that the term "deriving" is unclear. Applicant respectfully traverses the rejection.

By the terms of the claim, the cells are not "derivatized." They are, however, "derived" from the cancer or non-cancerous proliferative disease being treated in the recited method. This meaning of the claim term at issue is clear, particularly when read in light of the specification at page 19, line 27, *et seq.*, for example.

CONCLUSION

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is respectfully requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: 2-7-2008

By: _____

DANIEL A. MONACO
Registration No. 30,480
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
(215) 988-3312 - Phone
(215) 988-2757 – Fax
Attorney for Applicant